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Role of S100 Proteins in Cancer

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ABSTRACT:
Therapy to cancer is one of the greatest challenge world faces at present despite of few existing treatment modalities. In order to effectively contribute to cancer therapy, understanding of cancer markers and role of the markers in cancer formation at molecular level are vital. Past two decades, one such markers made center stage is S100 proteins which have been also implicated in tumerogenesis. This review pays much attention on the role of S100 proteins in different cancer at molecular level. Cancer of different organs linked to different S100 family proteins, which show varying mechanism of actions. To the best of our knowledge, we reviewed several journals and article related to S100 proteins and role which play on the cancer formation. Although, some of the S100 proteins role has been established and some hypothesized in tumerogenisis, further research work is in progress to unravel the mystery behind cancer formation.

Key Words: Tumerogenisis, S100 proteins, intracellular, extracellular

INTRODUCTION

Mammalian cells express more than 30,000 genes. These gene expressed in cancer cell is different from normal cell because of its distinct fuction and morphology of cancer cell. So mutation takes place in the normal cells genes which leads to tumor formation. The abnormal cells are expressing various mutated proteins. One such protein is called S100 protein which is promising in diagnosis and treatments of several pathological conditions (Table 2). S100 proteins play important role in several disease conditions. Till date, there are 20 known human S100 proteins of which 16 of the genes cluster to chromosome 1q21 (Table 1). S100 gene expression is found in the vertebrates, on the other hand it is absent in invertebrates. The conserved S100 gene structure contains three exons and two introns, of which the first exon is noncoding one [1]. According to the structural properties of S100 proteins, this is divided into three groups. They are a) approximately 200 members of the calmodulin-S100-troponin C superfamily, which contain high affinity EF-hand type calcium-binding domains, b) those containing a hemolysin-like calcium-binding domain and c) the annexin family, which bind phospholipids in a calcium-dependent dependent manner [2].

Recent research works show that S100 proteins association with different biological and disease conditions. Specific S100 proteins are found expressed in specific cancer of different organs. Surprisingly, few of S100 proteins such as S100A2, S100A11 and S100 A9 are functioning as tumor suppressor. However, some other S100 proteins are functioning as tumor promoters [1]. These behaviors of S100 proteins show intricacy and unpredictable functioning of the group. It was also found that most of the proteins regulate p53 transcription factors leads to promoting metastasis [2]. The detection and research on S100 would assist in diagnosis, monitoring and as a possible therapeutic target. A number of Sl00-related small calcium-binding proteins have been identified in mammalian cells. Although their functions are still vague, they are thought to mediate calcium signals in normal and transformed cells and play

important roles in many biological events. This review mainly focusing on, expression, mechanism of expression, and the role of S100 proteins in cancer transformation, which will assist in better understanding of disease process, treatment modalities, diagnosis, monitoring as well as indentifying possible therapeutic targets.

Structural Property of S100 Protein

S100 protein is an acidic protein ranging from 10-12kDa. S100 proteins are low molecular weight protein with exception of some high molecular weight proteins such as profilaggrin, trychohyalin and repetin [3, 4]. "S100" name comes from it's solubility in 100% ammonium sulphate [5]. S100 proteins consist of calcium binding two EF-hand motifs. EF hand is a helix-turn-helix structural motif in proteins. It consists of two alpha helices positioned roughly perpendicular to one another and linked by a short loop region (generally 12 amino acids) that often binds calcium ions. One common EF-hand to S100 proteins on the C-terminal portion and one specific to this family located at the N-terminus. Subsequent to the C-terminal EF-hand region is a stretch of amino acids referred to as the C-terminal extension. This stretch of amino acids shows most variability between the different S100 proteins [3, 4].

In S100 proteins, the C-terminal extension and hinge area have the most variability between the different proteins and hence responsible for their specific biological properties. S100 proteins bind to different target proteins to exert their activities. Experimental evidences confirm that the hinge region and the C-terminal extension play a critical role in the interaction of S100A1, S100B, S100A10, and S100A11 with several target proteins [6]. There are three factors contribute significantly to target selectivity: molecular architecture, response to binding of Ca2+ ions, and the characteristics of target binding surfaces [122].

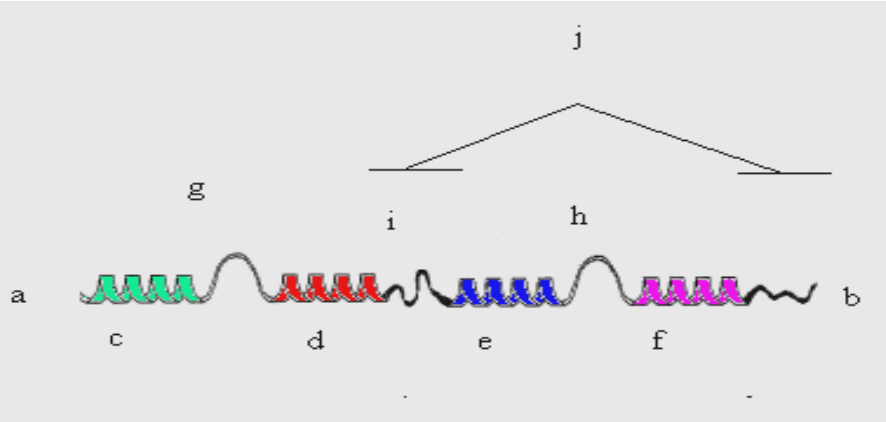

Fig.1 Secondary structure of a S100 protein

a-N-Terminal, b-C-Terminal, c,d,e,f are alfa helices, g,h are Ca2+ binding region, i-hinge region, j- least amount of sequence homology. (Reference 6)

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The EF hand motif was among the first structural motifs whose sequence requirements were analyzed in detail. The calcium ion is bound by both protein backbone atoms and by amino acid side chains, specifically those of aspartate and glutamate. Five of the loop residues bind calcium and thus have a strong preference for oxygen-containing side chains, especially aspartate and glutamate. The sixth residue in the loop is necessarily glycine due to the conformational requirements of the backbone. The remaining residues are typically hydrophobic and form a hydrophobic core that binds to stabilize the two helices (Fig.1).

The two Calcium binding sites in an S100 protein bind Ca2+ with different affinities, a higher affinity in the case of the C-terminal site and a much lower affinity in the case of the N-terminal site [2, 7, 8, 109]. In human, there are 20 members that have 22% to 57% sequence identity, and vary between 79 and 114 amino acid residues in length. Further diversities are achieved by different metal ion-binding properties of the individual S100 proteins, spatial distribution in specific intracellular compartments or in extracellular space, and their ability to form homo and heterodimers [9]. Some conserved regions are also present in the c-terminal extension and hinge region which demonstrate that common cellular function for all S100 proteins [8].

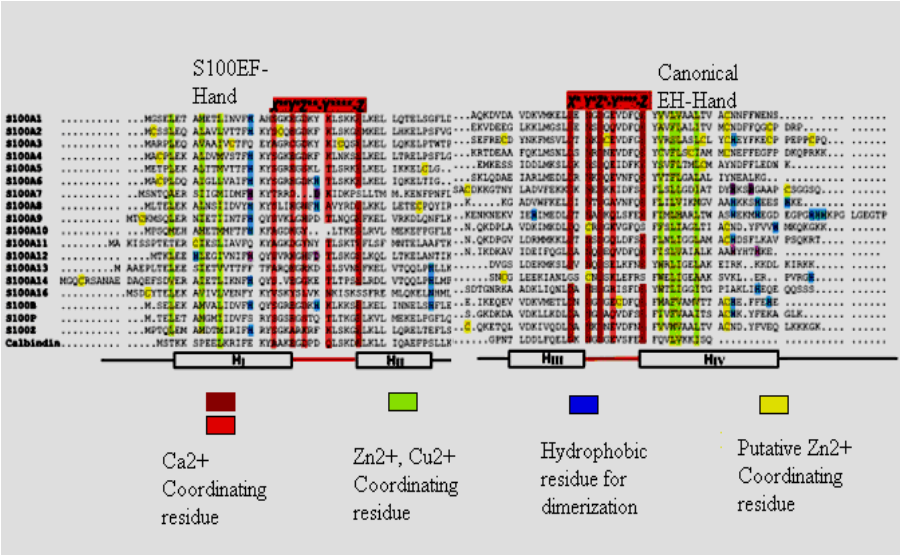

Fig.2 Human S100 proteins sequence arrangement (Reference 1)

Nuclear magnetic resonance (NMR) spectroscopy, X-ray crystallography, and multiple anomalous wavelength dispersion experiments confirm the S100 proteins existence as a homodimer, which are bound by a covalent bond [10-19]. A number of S100 proteins form heterodimers, as is the case with S100A1/S100B, S100A8/S100A9, S100B/S100A6, S100A1/S100A4, and S100B/S100A11 dimers [20-25]. Most of the S100 proteins undergo confirmational changes upon calcium binding which leads to the structural alteration. This alteration makes helices IV and III forms perpendicular to each other. These regions are important for the recognition of S100 target proteins. Target proteins for S100 have been identified for some of the S100 proteins. Some of the target proteins include CapZ, GFAP, desmin, vimentin, tubulin, p53,

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Table1 represents the gene name, obsolete name, chromosomal location and sequence accession ID (reference 1, 6, 8, 9 and 34)

Gene Name	Chromosomal location	Sequence Accession ID	Other and Obsolete Names nanaNames
S100A1	1q21	NM_006271	S100A, S100
S100A2	1q21	NM_005978	S100L,CaN19
S100A3	1q21	NM_002960	S100E
S100A4 (metastasin)	1q21	NM_002961	MTS1, CAPL, p9KA, pEL98, 18A2, 42A
S100A5	1q21	NM_002962	S100D
S100A6 (calcyclin)	1q21	NM_014624	CACY, 2A9, CABP, 5B10, PRA
S100A7 (psoriasin)	1q21	NM_002963	PSOR1
S100A7A	1q21	NM_176823	S100A15, S100A7L1
S100A7L2	1q21		S100A7b
S100A7P1	1q21		S100A7L3, S100A7d
S100A7P2	1q21	----------	S100A7L4, S100A7e
S100A8 (calgranulin A)	1q21	NM_002964	CAGA, MRP8, P8, CGLA, MIF, NIF, L1Ag, MAC387, 60B8AG, CFAG
S100A9 ((calgranulin B)	1q21	NM_002965	CAGB, MRP14, P14, CGLB, MIF, NIF, L1Ag, MAC387, 60BAG, CFAG
S100A10 (annexin II ligand; calpactin I)	1q21	NM_002966	Annexin II ligand (ANX2LG), calpactin I, light polypeptide (CAL1L), p11, CLP11, 42C
S100A11 (calgazzarin)	1q21	NM_005620	Calgizzarin, S100C
S100A11P (S100A11 pseudogene)	7q22-31		S100A14
S100A12 (calgranulin C)	1q21	NM_005621	Calgranulin C (CAGC), CAAF1,
S100A13	1q21	NM_005979	
S100A14	21q22	NM_020672	BCMP84, S100A15
S100A16	1q21	NM_080388	S100F, DT1P1A7, MGC17528
S100B	21q22	NM_006272	S100-beta
S100P	4P16	NM_005980	S100A7L1, S100A7a
CALB3 (calbindin 3)	Xp22	NM_0004057	Calbindin D9k, CaBP9k, CABP1

GAP-43 (neuromodulin), neurogranin, PKC and caldesmon [6, 26-31].

Function of S100 Proteins

In general, S100 proteins exhibit pleiotropic effect in different cell types. The effects include regulation of protein kinase C phosphorylation, regulation of energy metabolism by modulating the activity of several target enzymes, and regulation of cell shape through influence on polymerization condition of cytoskeletons microtubules, actin filaments and intermediate filament. In addition, S100 protein binds to protein kinase target annexins which is linked to in intracellular signal transduction. Several diseases are linked to varying cellular concentration of Ca2+. Disease conditions include Alzheimer's disease and neoplastic diseases etc., First report of S100 proteins association with disease condition was reported for s100A8 and s100A9 proteins, in so-called cystic fibrosis antigen [7]. Calcium dependant signal transduction based on the activation of membrane receptor leads to increase in intracellular Ca2+ concentration. This calcium binds to the EF-hand proteins, which transmit the signal by modifying specific target proteins. Then the altered

Table 2 indicates Human non cancerous diseases associated with S100 proteins (Reference 1)

PROTEIN	DISEASE
S100A1	Cardiomyopathies
S100A7S100A7L1/A15	Psoriasis
S100A8,S100A9,S100A12	Inflammatory Disorder
S100B	Neurodegeneration

target proteins exhibit cellular response to the stimulus [7]. One exception is that S100A10 protein does not bind with ca2+, but binds with annexin intermediate filaments to form tight complex, which is thought to be involved in endo- and exocytosis. There is also relation between frequent rearrangement of S100 gene cluster in chromosome region lq21 and tumerogenisis.

Mechanism of Action in General

Upon calcium binding to S100 proteins, leads to a conformational change in these proteins that expose amphiphilic amino acid residue which is the binding site for target proteins.Calcium binding to the S100 preotein is vital in the interaction of binding of target proteins [2]. Gao. Z. H et al, research on calmodulin interaction with its target led to hypothesize that each target protein may interact with a unique binding site [32]. A unique feature of these proteins is that individual members are localized in specific cellular compartments from which some are able to relocate upon Ca^{2+} activation, transducing the Ca^{2+} signal in a temporal and spacial manner by interacting with different targets specific for each S100 protein. Some members are even secreted from cells exerting extracellular, cytokine-like activities partially via the surface receptor RAGE (receptor for advanced glycation end products) with paracrine effects [33].

Role of S100 Proteins at Intracellular Level

Both at intracellular and extra cellular level, S100 proteins play different roles. Intracellular functions comprise of regulation of protein phosphorylation, enzyme activity, calcium homeostasis, cytoskeletal components and transcriptional factors. For instance, both S100A4 and S100B are thought to inhibit p53 phosphorylation leading to inhibition of its transcriptional activity.

S100 protein interaction with target proteins depends on the amino acid sequence of the individual S100 regions

Table 3 S100 proteins functions and possiblecancer diseases (references 1, 6, 8, 9 and 34)

Gene Name	Intracellular Functions	Extracellular Functions	Nuclear Function	Cancer Disease
S100A1	Regulation of calcium Homeostasis, Cytoskeleton components, Enzyme Activity, cell survival, Proliferation and differentation			Renal
S100A2	Regulation of cytoskeleton components		Yes	Thyroid, Melanoma, Breast, Prostate, Lung
S100A4 (metastasin, calvasculin)	Regulation of calcium Homeostasis, cytoskeleton components, protein phosphorylation	Induction of apoptosis S100A4	Yes	Thyroid Melanoma, Breast, Prostate, Gastric, Colorectal,Bladder
S100A6 (calcyclin)	Regulation of cytoskeleton components			Breast, Colorectal
S100A7 (psoriasin)	Regulation of cytoskeleton components, cell survival, proliferation and differentation	Chemoattractio n for leucocytes		
S100A8 (calgranulin A)		Macrophage Attraction, Chemoattractio n for leucocytes		Colorectal, Breast, Gastric
S100A9 ((calgranulin B)	Regulation of cytoskeleton components	Macrophage Attraction, Chemoattractio n for leucocytes		Breast, Colorectal, Gastric
S100A11 (calgazzarin)	Regulation of enzyme Activity, cell survival, Proliferation and differentationn			Bladder, Prostate, Gastric, Colorectal, Breast, Renal
S100B	Regulation of calcium Homeostasis, enzyme activity	Stimulation of neurite outgrowth S100B	Nuclear Functions	Melanoma

participating in the formation of the binding surface, differences in the orientation of helices in individual S100 proteins, and/or structural characteristics of target proteins. Most of the S100 family members have a role in modulating cytoskeletal dynamics.

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Again they display remarkable diversity of function, exhibiting direct interaction. Some of these interactions have been concerned in mediating metastasis. S100 proteins play a role in modulating proliferation, with both S100A1 and S100A11 shown to inhibit cell proliferation [34]. For most of the S100 proteins the target proteins have been well-known, but there are S100 members for which target proteins remain to be identified. A certain degree of cell specificity exists for any S100 member; however a few cases S100 proteins share their target proteins in different cell types and hence, regulate identical activities [6]. In addition, different S100 proteins are involved in different human disease conditions. Calmodulin is the most prevalent Ca^{2+}-sensing protein, found in all eukaryotic organisms including yeasts.

Extracellular Function

Although the secretion of S100 proteins outside the cell is remains to be known, there are few hypotheses regarding the secretion are available. The likelihood of the secretion of S100 protein by upon calcium binding to the protein, the hydrophobic region at the amino acid terminals is exposed. So the exposed region is reacting with the membrane protein and gets excreted to the extracellular level. At extracellular level, multimeric rather than dimeric form of S100 proteins reported to shown the activity. Multimeric form of S100 proteins are S100A12, S100A4, and S100B. This polymeric form of S100 proteins bind to RAGE receptor and exhibit its intracellular signaling cascade [35]. While the cellular effector proteins have yet to be determined for most of the members of the S100 family,

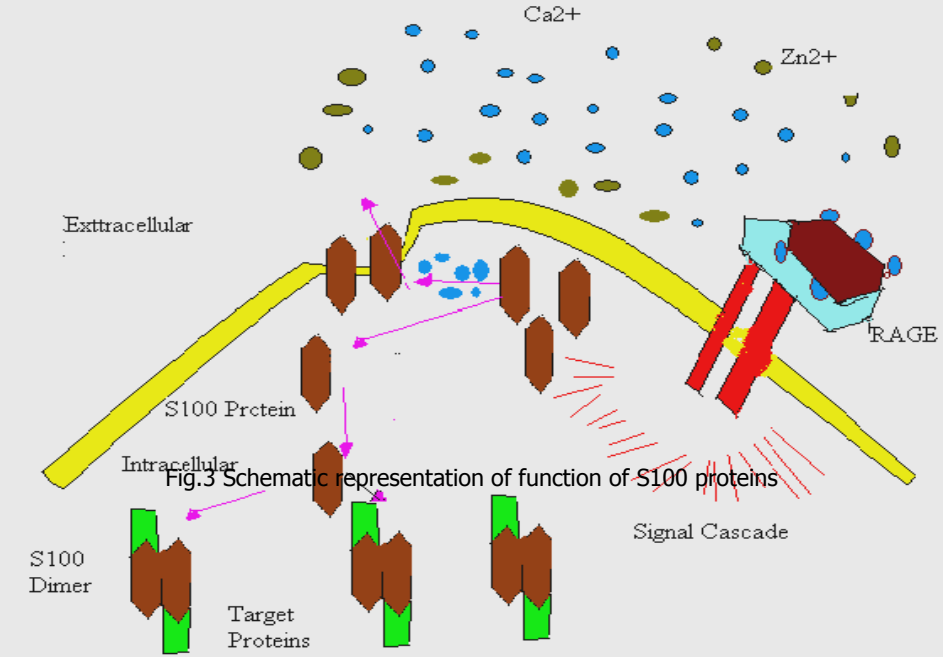

Fig.3 Schematic representation of function of S100 proteins

At extra cellular level, in presence of more amounts of Ca2+ and Zn2+, multimeric S100 proteins bind to RAGE receptor. At intracellular level, S100 dimers regulate biological activity by binding to their target proteins. The binding surfaces located on opposite sides of S100 proteins dimer recognize the target proteins. In this way, S100 dimer binds with two homologous or heterologous target proteins

recent findings indicate that cytoskeletal elements are most likely to be involved for the response to S100 proteins. For instance, Rosario Donato observed invasiveness of metastatic cells regulation of the dynamics of myosin filaments [6]**.** S100 proteins which are involved in tumor progression include S100A1, S100A4, S100A6, S100A7, and S100B, while S100A2 and S100A11 have been hypothesized to be tumor suppressor proteins [36]. Functioning parameters for S100 proteins are the serum and extracellular level of of S100 proteins, interaction of S100 protein with its receptor(s) in its target cell, and signaling pathways activated upon S100 binding to its receptor(s) are critical elements to illustrate the physiological relevance of extracellular activities of S100 proteins [6].

S100 Proteins in Cancer

S100 proteins implicated not only in cancer but also in other pathological conditions [2, 7, 8]. S100 proteins function by inhibiting the substrate protein phosphorilation, in which access of kinase to its substrate is prevented [24, 30].

S100A1

Guozheng Wang et al, found both S100A4 and S100A1 are expressed in same cultured mammary cell which signifies that S100A1 might modulate the metastasis-inducing capability of S100A4 [23]. S100A1 functions in cell include regulation of calcium homeostasis, cytoskeleton components, enzyme activity, cell survival, proliferation and differentiation. This protein has been implicated in renal carcinoma [23]. Both S100A1 and S100B expression have been documented in pathologic conditions involving unregulated cell growth such as cancer. Increased expression of S100A1 level has been acknowledged in melanomas, thyroid carcinoma [2]. Sufficient spectroscopic data indicate that S100A1 and S100B dimers undergo a conformational change as Ca2+ ions are loaded. For both subunits, this conformational change can also be induced when the pH is raised from 6 to 8.3 [2]. All the results support the possible role of S100A1 and S100B dimer in cancer.

Decreased cell proliferation through increase in the tubulin levels by inhibition of S100A1 synthesis has also been reported in PCL2 cell line. The increase in tubulin levels is due to an increase in unpolymerized tubulin at constant levels of polymerized tubulin [37]. The above mentioned observation is supported by the inhibitory effect of S100A1 on tubulin assembly. S100A1 cause aggregation of vimentin IFs as a result of MT disassembly reported in several cell lines [38]. Central portion of tubulin (Helix H8), the C-terminus of tubulin, and protofilament forming region [39] are implicated in binding site for S100A1. This result substantiates the likelihood of S100A1 in regulation of MT dynamics which might be implicated in cancer transformation.

In neuronal cell, S100A1 binds to synapsin I and II [40] proteins to anchor synaptic vesicle to F-actin, which is implicated in nerve signal transmission in brain nerve terminals. On the other hand, role of the interaction between S100A1 and synapsin in PCL2 cell is yet to be found [41]. Further research work is necessitated to unravel the mystery behind the interaction. Van Eldik et al, observed that regulation of gap junctional permeability by the Ca2+ dependent interaction of S100A1 protein with junctional polypeptide. [42]. It is also found that interaction of intracellular Ca2+ with the S100A1 leads to communication between transformed cells. Additional research work on gap junctional intracellular communication in hepatic cell carcinoma led to hypothesis that the regulation of cell-cell cormnunication by S100 protein linked to cell growth since the changed cell-cell communication profile in transformed cells. Sch fer and Claus W. Heizmann have put forward a proposition that general model for function of S100 proteins based on

modulating effect of calmodulin. An interesting recent demonstration is that calmodulin and S100A1 are capable of binding to tran- scription factors of the helix-loop-helix family, thereby modulating the DNA binding capabilities [8].

S100A2

The S100A2 (also known as CaN19 or S100L) gene was first recognized by means of subtractive hybridization screening. More attention was paid on S100A2, because of its differential expression during transformation and metastasis in various tumors. Significantly reduced level of S100A2 has been shown in breast tumor biopsies, melanomas, esophageal, and other cancer types which are related to the prognosis of certain cancers [43]. As a result, expression of S100A2 was proposed as a valuable prognostic marker. D Liu et al, result suggests that the loss of S100A2 is associated with the development of malignant cells and is not associated with early tumour development [44]. On the contrary, S100A2 overexpression was recently found to correlate with prognosis in ovarian, gastric, and lung cancers. As a whole, role of this protein in tumerogenisis remains vague [43]. Rolo of S100A2 as a tumour suppressor in some cancers and as a tumour promoter in others is identified. S.W. Lee et al reported that S100A2 may have tumor suppressor function. In support of the hypothsis, R. Wicki et al shown that promoter region of S100A2 gene unmethylated in normal cell, but hypermethylaed in tumor cells [45-47]. In addition S100A2 may also reduce cyclooxygenase-2 (Cox-2) expression, because Cox-2 up-regulation is associated with tumourigenesis in many cancers [43]. A research on S100A2 proteins found that the expression of S100A2 decreased in malignant head and neck epithelial cells and tissues compared with normal keratinocytes, whereas a Villaret et al, found this gene to be overexpressed in malignant head and neck carcinomas compared with normal oral mucosa [48]. A number of expression studies that have implicated S100A2 as a breast tumour suppressor gene [54].The reason for this inconsistency of S100A2 protein expression is not clear.

The role of S100A2, if any, in the cell cycle is not known. But Gang Feng et al, proposed that S100A2 can be regulated by the tumor suppressor p53, and because p53 is known to mediate apoptosis induced by DNA damaging agents. The loss of S100A2 may contribute to increased resistance to apoptosis. This implies that S100A2 as a tumor suppressor. The mechanism behind the suppression of S100A2 expression was shown to involve, at least in part by hypermethylation of the gene in tumorigenic HBE cells and in most of the NSCLC cell lines. Expression profile of this protein in several cancers also indicates that it is a candidate class II tumor suppressor gene. Among the tissues and cell lines previously examined (breast, cervical, skin, oral), the S100A2 expression is high in normal cells and low in cancer cells [49, 50]. Oligonucleotide array, quantitative reverse transcription–polymerase chain reaction and western blot analyses of both lung adenocarcinoma and bronchiolar epithelial cells (SAEC and NHBE) revealed that S100A2 and S100A4 were the most strikingly downregulated and upregulated members of the S100 family, respectively. Immunohistochemical analyses of lung adenocarcinomas showed that positive S100A2 expression was significantly associated with lymphatic invasion and positive S100A4 expression with vascular invasion. Immunohistochemical analysis further confirmed high levels of S100A2 in benign tissues and a progressive loss with increasing tumor grade [51]. These results suggest that downregulated S100A2 protein associated with tumor formation and further slight increase in the expression implicated in tumor invasion.

There have been exceptions to the inverse correlation between S100A2 expression and

malignancy. Kaplan-Meier analysis shows that patients whose tumors had positive S100A2 expression had a significantly lower overall survival and disease-specific survival rate at 5 years after surgery than did patients with negative S100A2 expression ($p < 0.001$ and $p < 0.001$, respectively) [52]. By suppression subtractive hybridization method, more than three times higher in immortalized AAH cell line (PL16T) and a human non-neoplastic bronchial epithelial cell line (PL16B) analysed for transcription levels, results showed encoded S100 calcium binding protein A2 (S100A2). In normal lung tissue, both TACSTD2 and S100A2 were expressed at very low levels [53]. According to Teresa Knapp1et al, analysis on the expression of this gene in lung cancer differs from the earlier report by demonstrating a consistent and strong over-representation of this gene in multiple lung tumour samples [54]. Real-time reverse transcription-polymerase reaction analysis on 72 in Barrett's adenocarcinomas revealed frequent overexpression of S100A2 and S100A4 [55].

S100A4

S100A4 protein is also known as metastasin (p9Ka, calvasculin and mts-1 amongst other names), which is located on 1q21 chromosomes, encodes an acidic 101-amino acid protein containing two EF-hand motifs. It was identified by Jackson-Grusby and coworkers [57] and called 18A2. S100A4 gene has been implied to be involved in cell immortalization**,** cell growth differentiation of mammary epithelial stem cells to myoepithelial-like cells and fibrogenesis. Barraclough, R. et al, have identified metastasis-associated cytoskeletal calcium binding protein, S100A4 (p9Ka), as an inducer of metastatic capability in benign rat mammary epithelial cells. Both DNA transfer and induction of metastasis in vivo were used to identify S100A4 DNA sequence in non-metastatic mammary cells [58]. Increased expression of S100A4 at both protein and mRNA level has been associated with many malignancies such as bladder, breast, colorectal, thyroid, astrocytic, gastric, lung and prostate cancer [34, 59]. Keizo Takenaga et al demonstrated that the expression level of S100A4 is positively correlated with the invasive abilities of various clones established from Lewis lung carcinoma. S100A4 has been reported to be specifically expressed in metastatic tumor cells [56]. In addition, S100A4 is expressed in cells entering S phase of cell cycle [57]**.**

Mechanism of S100A4 in Cancer

Recombinant S100A4 has been reported to interact with cytoskeletal components and to form oligomers, particularly homodimers in vitro. Using the yeast two hybrid systems, association of S100A1 and S100A4 has been found. This led to hypothesis that S100A1 might influence metastatic ability of S100A4 [23]. On the other hand, S100A1 and S100A4 are colocalized in cultured Rama 29 cells, which do not express a metastatic phenotype [23]. Varying mechanisms have been proposed for tumerogenisis and metastasis in colorectal cancer. The mechanisms regulating S100A4 expression in colorectal epithelial cells are largely unknown. It has been reported that DNA methylation of the S100A4 gene plays a critical role in the expression of S100A4 [56]. In addition, the high expression of S100A4 in metastatic cells may be associated with the demethylation of a CD3S enhancer in the first intron of the murine S100A4 gene [56]. Gene transfer experiments have shown that rodent or human S100A4 is able to induce metastatic capability in non-metastatic breast tumour cells [60]. Increased expression of S100A4 is closely associated with the process of metastasis in several human solid cancers including gastric cancer, colorectal adenocarcinoma and breast cancer. It was suggested that over-expression of S100A4 is closely correlated with a number of factors for tumor aggressiveness, such as lymph node metastasis, depth of invasion, and peritoneal dissemination**.** It has also been

put forward that, the protein may exert its effect on metastasis formation not only by stimulating the motility of tumor cells but also by affecting their invasive properties through deregulation of the extracellular matrix [61].

In colorectal adenocarcinoma, S100A4 has been associated immunofluorescently with the actin/myosin cytoskeleton in fixed cells. Calcium-dependent interaction of S100A4 with actin tropomyosin and non-muscle myosin has been reported [23, 61, 63, 64]. Osteosarcoma cell lines with mutant beta-catenin expressed up to 60-fold elevated S100A4 levels, and exhibited strongly increased cell migration and invasion. Surprisingly, invasion and migration were knocked down by S100A4 siRNA and beta-catenin siRNA. In addition to that, S100A4 cDNA transfection increased migration and invasion. S100A4 is a direct beta-catenin/TCF target, which induces cell migration and invasion in cell culture. So it is believed that, S100A4 plays vital role in the migration and invasion of osteosarcoma cell [62]. In cellular level, nonmuscle myosin molecules form bipolar filaments, which interact with actin filaments to produce a contractile force. Phosphorylation of the myosin plays a regulatory role in the myosin assembly. S100A4 (Mts1), the metastasis associated protein might also bind directly the L subunit of protein kinase CK2, thereby modifying the enzyme activity. Therefore, it is proposed that Mts1 modulates cell motility by regulating the phosphorylation of the myosin heavy chain [65, 66]. Upon to binding of S100A4 to the region of tropomyosin containing residues 39–107, provide Ca2+ sensitivity to tropomyosin regulation of actomyosin ATPase activity [66]. Sufficient research work on expression of S100A4 and antisense S100A4 RNA treatment in murine mammary adenocarcinoma cell lines and B16 melanoma cells indicate that role of S100A4 protein in metastasis phenotype [67, 68]. Another proposed mechanism in tumerogenisis is that binding of S100A4 to p53 which is a transcription factor and regulate cell cycle, leads to inactivation of tumor suppressor function of P53 [7]. In colorectal carcinoma, nuclear translocation of S100A4 protein may involve in the process of invasion and metastasis of colorectal cancer. It is reported that the possibility of S100A4 regulating transcription of other genes either through direct DNA binding to or through interaction with other DNA binding proteins [61, 59]. In case of breast and lung cancer, expression of RAGE (receptor for advanced glycation end products) was found, where abundant S100A4 and S100A6 expression were also observed. So, the possible interaction between the RAGE and the S100A4 in the development of these cancers was also suggested [36].

In oral squamous cell carcinoma, mRNA expression of E-cadherin was reversely correlated with S100A4 expression. Therefore, S100A4 mediated regulation of E-cadherin expression may play an important mechanism in invasion and metastasis of oral SCC. Expression of E-cadherin is down-regulated during the acquisition of metastatic potential at late stages of epithelial tumor progression [69]. Among the S100 protein family, S100A4 has multiple functions in cell cycle progression and cell motility for its ability to activate non-muscle myosin [69]. Human adenocarcinoma cell lines, which are expressing S100A4 reported to have invasive property, but not the S100A4 negative cell lines [56]. In bladder carcinoma, expression of the S100A4 protein has been shown to correlate with the risk of metastasis in both animal tumour-model systems and clinical investigations in other tumour types. Mads Agerbaek et al showed the immunohistochemical expression of S100A4 protein and associated with disease dissemination and reduced survival [70]. Consideration of clinical studies in conjunction with evidence from experimental animal models reveals that the calcium binding protein S100A4 and the the

cell cycle arrest/apoptosis-inducing p53 protein are amongst the most promising targets for therapy against metastatic disease in patients with bladder cancer [71].

The mRNA and protein level of S100A4 was significantly higher in high-grade cancer specimens compared with BPH, prostatitis, and low grade cancer. Studies have also shown that S100A4 exerts its metastatic effect by influencing matrix metalloproteinases, endogenous inhibitors, and tissue inhibitors of metalloproteinase, in a way that facilitates extracellular matrix destruction [49]. Mohammad Saleem et al, demonstrated that the S100A4 gene controls the invasive potential of human CaP cells through regulation of MMP-9. Overexpression of the S100A4 gene increases the invasiveness of CaP cells and that its suppression reverses this effect and hypothesized that the S100A4 gene influences the ratio of MMP-9 to TIMP-1, leading to ECM degradation [72]. When anti-S100A4 ribozyme transfected into osteosarcoma cells, shown to reduce the expression of matrix metalloproteinases and induce expression of inhibitors of these enzymes, resulting in reduced invasive potential [123]. S100A4 also interacts with the sarcoplasmic reticulum and with actin stress fibers in a Ca2+-dependent manner, resulting in the regulation of cell deformability and morphology [73]. In Barrett's Adenocarcinomas, S100A2 and S100A4 are overexpressed in cytoplasm of the cell. Further studies are ongoing to understand the biological significance of these S100A4 proteins in Barrett's tumorigenesis [55]. Different form of expression of S100A4 in cellular level, the expression was linked to the metastasis of the particular cell type. The expressions are pEL98 [57], which is an mRNA induced in transformed murine cells, an overexpressed gene product in metastatic tumor cell subclones, P9K which is an induced protein product in differentiated mammary epithelial stem cells. Although different mechanism has been reported, detailed study is necessitated to clearly understand the exact mechanism of tumor formation and metastasis.

Extracellular role of S100A4 include neuritogenic and angiogenic activities. Extra cellular S100A4 treatment decreases both the amount of polymerized F-actin and the levels of expression of RhoA, mDia and profilin. In addition, S100A4 decreases Cdc42 and N-WASP expression, but Rac1 expression remains unchanged [62]. These all characteristics lead to stimulation of cell motility. S100A4 is involved in tumor progression, cell migration and metastasis. Ambartsumian et al. also showed that S100A4 is capable of enhancing endothelial cell motility in vitro [62].

S100A5

S100A5 was identified while analyzing the sequence of gene cluster placed at human chromosome 1, where the S100A5 gene organized into four exons and three introns. The third and the fourth exons code for the two EF-hands and correspond to the second and third exons in the other S100 genes. Exon II of the S100A5 gene codes for 13 of the additional 18 amino acids, which are not present in other S100 proteins. This protein has a Ca2+ affinity 20- to 100-fold higher than the other S100 proteins studied under identical conditions. This protein also binds Zn2+ and Cu2+, bind strongly which impairs the binding of Ca2+ [2]. This protein is expressed in very restricted regions of the adult brain. Significance of this proteinin cancer is not clear.

S100A6

Human S100A6 gene, encodes an acidic 90-amino-acid protein (M_r 10.5) containing two EF-hand motifs. The gene product has been implicated to be involved in growth of hair follicles, differentiation, regeneration, secretion, and metastasis in mammalian cells [74]. S100A6 is mainly expressed in tissues from melanoma (66%), lung (69%), and colonic (65%) cancer patients [36]. In

colon cancer cell lines, S100A6 varients has shown to be differentially expressed. By using an immunoblotting approach, J. StulõÂk et al, detected four S100A6 variants with M.wt of 10 kDa isoform I II III and IV were deferentially expressed in the analysed colorectal carcinoma samples [74]. Expression of S100A6 isoforms I and III in malignant tissue, and on the other hand, an increased level of S100A6 isoform IV in healthy tissue was also reported in colon cancer cell lines.

The possibility of S100A6 variants might be due to the posttranslational modifications such as phosphorylation, acetylation, formylation or S-sulphation, which was described for some members of S100 protein family. J. StulõÂk a et al reported that the post- translational modification of S100A6 will induce the conformational changes which direct the binding of S100A6 variants to a specific target, and, thereby elicit a distinct cascade of cellular events. Increased levels of S100A6 production with premalignant tissue was also observed for preneoplastic lesions in human lung and might be of prognostic significance in these tumour types [74]. There is also a report for S100A6 and S100A4 implicated in invasion and metastasis of Human colorectal adenocarcinoma [75]. On the contrary**,** differential expression of S100A6 and S100A4 is reported in colorectal adenocarcinoma and the S100A6, rather than S100A4, is associated with human colorectal adenocarcinoma tumorigenesis and invasion/metastasis [76].

Although no functional implication has been estabilished, however biochemical studies on S100A6 have been shown to be specifically interacting with annexin, tropomyosin, caldesmon, and other proteins. Another link between S100 family members and tumorigenicity comes from the location of the S100 gene cluster, because the chromosome region 1q21 is frequently rearranged in various tumors, especially in human breast carcinomas. S100A6 expression may be linked to the progression of colorectal neoplasms [77]. The search for marker in osteosarcoma cell lines led to findings that S100A6 is commonly overexpressed in human osteosarcoma, loss of its expression correlates with a metastatic phenotype. Luua et al provided evidence that, S100A6 is commonly overexpressed in human osteosarcoma, loss of its expression correlates with a metastatic phenotype. Overexpression of S100A6 inhibits the cell migration and anchorage-independent growth of human osteosarcoma cells, suggesting that S100A6 may play a role in regulating osteosarcoma metastasis. Exact functional role of S100A6 proteins in cancer is not known completely. It has been shown to interact with the actin cytoskeleton via tropomysin [78]. It has been postulated that through its interactions with the actin microfilament system, S100A6 can modulate cell adhesion, cell motility, and/or anchorage independent growth [78].

S100A7

S100A7 is also known as psoriasin, M.W 11.3 kDa. The protein is highly abnormally expressed in invasive breast cancer cell lines, squamous carcinoma and psoriatic keratinocytes. S100A7 plays a vital role in breast cancer cell lines as immune response gene. This protein also acts as a host defense protein in partially burnt patient [79]. Some cellular factors contribute for the increased expression of the protein. Those factors are ECM loss, growth factor deprivation and cofluency [80].

In the breast cancer, Psoriasin gene is frequently overexpressed in preinvasive ductal carcinoma in situ (DCIS) relative to adjacent invasive carcinoma, suggesting a role in tumor progression [81]. Role of S100A7 in breast cancer has been revealed after the identification of down reguelation of psoriasin cDNA expression in a nodal metastasis relative to a primary breast tumor [82]. In breast tumors, higher levels of psoriasin measured by reverse

transcriptase-polymerase chain reaction and Western blot results suggest that psoriasin may be a marker of aggressive behavior in invasive tumors [82]. High psoriasin expression in human IBC (Inflammatory breast cancer) is associated with increased angiogenesis and worse clinical outcome, and psoriasin mRNA levels are coordinately regulated with VEGF and other genes related to hypoxia and mitochondrial reactive oxygen species (ROS) [83]. Psoriasin expression may be connected with a worse prognosis in estrogen receptor-negative invasive ductal carcinomas and raise the possibility that psoriasin expression may also be an indicator of risk of progression in ductal carcinoma in situ [84]. Psoriasin protein was found to be expression in intracellar level. In addition it is secreted in extracellularly. In association with its secreted nature, there is evidence that psoriasin can function as a chemotactic factor for CD4+ lymphocytes in the skin. Further, it has been implicated in the antibacterial defense mechanism of the skin [83]. In addition, the protein also related to the metastasis of sqouamous non small cell lung carcinoma which was confirmed using two-dimensional electrophoresis (2-DE) followed by a tandem mass spectrometer with a matrix-assisted laser desorption/ionization (MALDI) source. Ethan D. Emberley et al, reported as S100A7 promotes renal carcinoma cell migration has shown to be capable of promoting migration of renal carcinoma cells, suggesting an unproven but prospective mechanism for psoriasin to influence invasiveness [84].

Expression of psoriasin in skin cancer cell implicated S100A7 as an independent marker in skin cancer [85]. Based on a study, psoriasis is linked to 2.5-fold increased risk for nonmelanoma skin cancer in men and women, with no preponderance of any specific histologic subtype of cancer. Overexpression and interaction of S100A7 with the epidermal type fatty acid-binding protein (E-FABP) has been reported in human keratinocytes. This E-FABP protein is implicated in the intracellular transport of fatty acids. In the past, speculations were made about a role of S100A7 interaction in the pathogenesis of psoriasis [86, 87]. Ethan D. Emberleyet al, found that psoriasin physically interacts with Jab1 (c-jun activation-domain binding protein 1), a component of the COP9 signalosome that is involved in multiple signal transduction pathways, including the regulation of E3 ubiquitin ligases and the JUN/AP1 transcription factor in the yeast two-hybrid assay. This interaction was confirmed by coimmunoprecipitation assay in breast cancer cells. Ethan D. Emberleyet al, then hypothesized that intracellular psoriasin influences breast cancer progression, enhanced tumorigenesis and metastasis and that these may occur through stimulation of Jab1 activity [80, 88]. Further research work is required to unravel the mystery behind the interactions and possible role of which in tumor formation. Overexpression of psoriasin in MDA-MB-231 breast cancer cell was shown to influence the intracellular distribution and activity of Jab1 and enhance tumorigenesis and metastasis [83]. Using yeast two-hybrid screen, psoriasin was also found to interact with RanBPM, a RANGTP binding protein localized to the centrosomes, but the physiologic relevance of the association of psoriasin with RanBPM is undefined [80]. Colocalization of S100C and psoriasin gene to human chromosome 1q21-q22, was found to be expressed in most tissues and some cancer cell lines. So S100C prtotein was also implicated breast carcinoma. But the exact function of this co-localisation is not known [89].

S100A8 and S100A9 proteins

S100A8 protein is known as myeloid related protein 8 (MRP8) and S100A9 is known as MRP14. These proteins show a divergent pattern of cell- and tissue-specific expression, subcellular localizations, post-translational modifications and affinities for bivalent cations. These proteins expression are found in nutrophils, monocytes,

keratinocytes, and inflammatory epithelial cells [93]. Calcium-induced (S100A8/ S100A9)2- tetramers were shown to play a role in tubulin polymerization and stabilization during activation of phagocytes. Besides, zinc binds these proteins with high affinity. These S100 proteins bind two Zn2+-ions per homodimer and the zinc-binding sites are formed by residues from both subunits. It was found that extracellular S100A8/S100A9 exhibits antimicrobial activity by chelation of zinc, which is necessary for growth of bacteria. But, neither S100A8 nor S100A9 shows antimicrobial activity [96]. Formation of non-covalently associated complexes is a prerequisite for biological functions and individual complex forms may exhibit different actions. So, thorough research on role of these complexes as well as separate entity on cancer is required.

S100A8 and S100A9 were secreted by prostate cancer cells, in which S100A8/A9 induced the activation of NF-kappaB and an increased phosphorylation of p38 and p44/42 MAP kinases. In addition, extracellular S100A8/A9 stimulates migration of benign prostatic cells in vitro. [91,96]. Hae-Young Yong and Aree Moon found that siRNAs for S100A8 and S100A9 inhibited matrix metalloproteinase (MMP)-2 expressions in SNU484 cells as substantiated by gelatin zymogram assay, immunoblot analysis and reverse transcription (RT)-PCR. These results exhibit that requirement of S100A8 and S100A9 in transcriptional activation of MMP-2 gene in gastric cancer cell (SNU484 cells). In addition his study discovered a functional contribution of S100A8 and S100A9 proteins to processes required for malignant progression including invasion, migration and proteinase expression in SNU484 human gastric cancer cells [92, 94]. Among the S100 proteins, S100A8 (calgranulin A) and S100A9 (calgranulin B) have been shown to be implicated in tumor development or progression [93]. Mueller, A., et al, reported that S100A9 relatively than S100A8 exerts a major contribution to the invasive and migratory phenotypes of SNU484 cells [95].

S100A8 Function

S100A8 (MRP-8) was purified from myeloid cells in 1987 by Gdink and coworkers and have been shown to inhibit casein kinase activity. Like S100B and S100A4, this protein can be secreted into the culture media and appear to regulate cell growth [9]. Tolson J. et al, reported that inflammation-associated high expression of calcium binding protein S100A8 (MRP-8, Calgranulin A) in tumour cells in contrast to normal urothelium, confirmed by by means of SELDI – TOF(Surface Enhanced Laser Desorption/Ionisation - Time of Flight) mass spectrometry (MS) [90]. Importance of this protein in cancer is not known yet.

S100A9 Function

Simillar to S100A8, S100A9 (MRP-14) was also purified from myeloid cells in 1987 by Gdink and coworkers and have been shown to inhibit casein kinase activity. S100A9, have long and flexible C-terminal extensions that may be required for a target interaction independent of the EF-hand. In general, the C-terminal part of S100 protein exhibit the highest sequence variation and might, therefore, contribute to the specificity of S100 proteins [9]. Importance of this protein in cancer is not known yet.

S100 A10

S100A10 protein also known as calpactin light chain, CLP11, annexin II light chain (Anx2LC), 42C and p10. It has 94-96 amino acids with the molecular weight of 10.944Kd. Interaction between (annexin II-S100A10) heterotetramer suggests that polar residues in the hinge region, helix III, the C-terminal Ca2+-binding loop and the C-terminal extension of S100A10 interact with polar residues in the annexin II core, and these interactions might be critically implicated in the stabilization of the

S100A10-annexin II interaction. Though, the role of S100A10 in cancer formation is not known, several research work[97], on fibroblast and chromaffian cells have shown that increase in the annexin II-dependent bundling of F-actin, ability of annexin II to stimulate GFAP assembly, and increase in capacity to bind to preformed GFAP Ifs, which is required for the cell strength and shape. Since S100A10 bear mutations in EF-hand structure, interaction with target protein occurs independent of calcium 2+ [6]. Upon S100A10 binding to p36 protein forms calpactin I which results in the inhibition of phosphorilation mediated by tyrosine kinases such as pp6tY and the EGF-receptor kinase. Based on its interaction with phospholipids, actin, in vitro promotion of adrenal chromaffin granule fusion, calpactin I have been hypothesized to regulate secretion and cell motility [2].

S100B

In 1965 Moore identified homodimer of S100B chain as "S100" protein. Human S100B gene is positioned in the chromosome 21q22.3. This proetein is reported to bind cu2+ at intracellular level [98]. S100B is most abundant in glial cells of the central and peripheral nervous systems as well as in melanocytes, adipocytes and chondrocytes. S100B monomers often form a homodimer. Considerable amount of S100B monomers are bound to membranes within the cell [99].

In case of cancer cells, S100B expression level is highest in grade IV melanoma and has been associated with the presence of metastases and reduced survival [6]. S100B protein is reported to be used in staging malignant melanoma, establishing prognosis, evaluating treatment success and predicting relapse [6]**.** This Marker is useful for detection of progression from localized to metastatic disease during follow-up and for monitoring therapy of advanced melanomas. Serum level of S100B related to the survival of melanoma patients. Normal conscentration of serum S100B protein shows longer survival than patient with high concentration of S100B proteins in melanoma cancer [100]. Circulating S100B levels very sensitively detect metastatic growth and S100B concentrations reflect tumor mass and assit in treatmentregimens [99]. Guy S. O. A. Missotten et al, evaluated significance of serum concentration of S100B uveal melanoma patients. He reported that the S100B serum concentration was not correlated with any investigated prognostic factor and was not of prognostic value itself but female patients appeared to have higher S100B concentrations than male patients [102]. An observation from a research work on metastasis in malignant melanoma confirms that the serum S100B concentration rises with disease progression, and that increased levels are often the first symptoms of recurrence [104]. Elevation of serum S100B is highly specific for melanoma recurrence. Decreasing S100B concentrations reflect response to therapy while increasing S100B concentrations indicate tumor progression [99, 105]. Protein S100B demonstrated a higher sensitivity, specificity, and diagnostic accuracy in the diagnosis of newly occurring metastasis compared with to the tumor markers AP, LDH, and RT-PCR diagnostics. S100B protein shows higher sensitivity to detect new metastasis than other tumor markers (29% for protein S-100B, 22% for MIA, 2% for LDH, 17% for AP, and 24% for RT-PCR). The diagnostic accuracy was best for MIA (86%) and S-100B (84%), whereas AP (79%), LDH (77%), and RT-PCR (72%) demonstrated lower values. In malignant melanoma S100B proved to be a more sensitive marker than LDH level [100].

Different reports are available for the role of S100B protein in tumor formation. One groups of researcher's state that S100B as a tumor suppressor. On the other hand, S100B also reported for the tumor promoter activity [106, 107]. There is very little information available regarding the mechanisms that regulate extracellular

release of S100B protein. 5-HT1A serotonin receptor activation does stimulate S100B release [2]. The extracellular function of S100B is mediated by binding to the cell surface receptor for glycation end product (RAGE) [99]. In extracellular level, there is a report of S100B protein prosurvival activity in glutamate treated neuronal cells. Upon binding of S100B protein with RAGE receptor, S100B stimulates neurite outgrowth by nuclear translocation of NF-κB and upregulation of expression of the anti-apoptotic factor, Bcl-2, in target neurons [108]. Wheather the same mechanism takes place due to extracellular level S100B protein in cancer cell yet to be analysed. In intracellular level, S100B protein associated with axonemal MTs, centrioles, basal bodies, the mitotic spindle, the centrosomes, and the center part of the midbody in telophase cells as well as with cytoplasmic MTs [8,110,111]. S100B transduces signal via inhibition of protein phosphorylation, regulation of enzyme activity and involvement in Ca2+ homeostasis. Furthermore, S100B protein is functionally involved in the regulation of cell morphology by interaction with elements of the cytoplasmic cytoskeleton. S100B is implicated in preventing excess tubulin polymerization, and/or in remodeling of MTs upon elevation of cytosolic Ca2+, which is resulted in the tumor suppressor activity [112, 38]. K.A. McClintock et al, also reported S100B role in MT dynamics [39]. In contrast to the above report, S100B inhibits calcium-dependent phosphorylation of p53 by protein kinase C in vitro. This can lead to suppression of the p53 tumor suppressor mechanism, which is of importance in melanoma as well as other tumors, resulting in uncontrolled tumor growth.

Recently, it has been reported that S100B and S100A6 form heterodimer in human melanoma has been reported recently [24]. The significance of the heterodimer formation is not known. Expression of S100 protein and hyperactivation of Ndr in melanomas has been reported [107]**.** To regulate cell division and cell morphology, S100B stimulate Ndr, a nuclear serine/threonine protein kinase [114]. M.A. Mariggio et al, reported apoptosis inducing role of S100B protein in PCL2 cell lines by increased conductance in L-type Ca2+ channels. Using a different model system the PC12 cell line, Fano and coworkers [115], have observed increase in Ca2+ with S100B treatment, which results in apoptosis rather than the neurite extension. S100B proteins at nanomolar concentrations act as a growth and/or differentiation factor, while micromolar concentrations are necessary for induction of apoptosis, signifying that different protein concentrations might be responsible for these diverse effects [7]. Further research work is warrented in demand to clearly understand S100B protein role in tumor formation.

S100A11 or S100C

S100A11 is an EF hand– type Ca2+ binding protein, also known as Calgizzarin and S100C.Its expression in cancer correlated related not only to rapid growth and accelerated metabolism. A few studies have been carried out to determine the in vivo and in vitro functions of the S100C. In human fibroblast cell, S100C act as a growth inhibitor and in keratinocytes cells, S100C function as a Ca2+-induced growth inhibitor [116, 118].

Although exact role S100A11 is not known clearly, M. Sakaguchi et al, have theorized to have tumor suppressor activity. This hypothesis was based on the observation that high expression of S100A11 in normal cell than tumor cell. This is further corroborated by microinjection of an anti-S100A11 antibody into normal confluent quiescent cells induced DNA synthesis [116]. Ashfaque Ahmed Memon found that a significant down-regulation of the S100C protein level in human bladder carcinoma cell line T24. In agreement with this result, S100C mRNA was low in the T24 compared with the normal RT4 cells. The down-

regulation of S100C in various cancerous tissues compared with their normal counterparts has been observed [117]. Furthermore, low expression of S100C has also been reported in immortalized human fibroblast cells as compared with normal fibroblasts [118]. Studies indicate that decreased expression of S100C is associated with increasing tumor aggressiveness and poor prognosis in bladder cancer patients [119]. This result indicates that tumor suppressor activity of S100C protein. Further it was found that, S100A11 gene expression was associated with the development of lymph node metastases. S100A11 gene expression was clearly up-regulated in specimens from patients with lymph node metastases relative to those from patients without lymph node metastases [120]. In contradiction with the above results, expression of calgizzarin was much higher in colorectal cancer than in normal colorectal mucosa [121].

CONCLUSION

S100 proteins show variation in structure, expression in different cancer tissue/cell, metal ion binding and dimer formation ability. In genomic level, S100A2 to S100A6 proteins are in a subcluster proved to be responsible for tumerogenesis. Eventhough, some of the functions of S100 proteins have been mentioned in this review, several questions are needed to be addressed before entering to conclusion.

Intra cellular level S100 proteins exert different role in calcium dependent manner. Distinctive feature of each of the S100 protein is lacalization at different cellular organells. Upon binding of calcium to the intracellular dimeric form of homologous and heterologous S100 proteins, binding sites are exposed for specific target proteins which lead to singnal transduction to effector proteins. Target proteins for some of S100 protein have been identified, which are shown to be involved in specific as well as common target to exert S100 protein functions. With the help of genetically engineered animal models, several research works are underway to study the function of S100 proteins at extra and intra cellular level in normal as well as pathological conditions. It is require analysing the exact function and specific target protein for the each members of S100 familly protein is required in cancer pathogenesis.

Extra cellular function S100 protein depends upon concentration of the protein, which regulates cell or tissue organization in varying pathogenic state. Some of the S100 proteins act from outside of cells to remodel tissue at particular pathological conditions. Especially, S100B and S100A12 interact with extracellular RAGE receptor to transducer signal at intracellular level. Importantly, certain questions need to be addressed before understanding of function of S100 proteins at extracellular level. At first, search on factors inducing S100 protein secretion/ release in particular cancer, and after the release of the protein, it also necessary to identify target (receptors) proteins in which the S100 proteins exert their action.

Extra cellular role of each S100 proteins and its specfificity against the RAGE receptor or with other receptors will pave the way for understanding of each proteins role in cancer formations. Further research work is necessitated, in order to understand the relationship between extracellular activities of S100 proteins and their effect at intracellular level in cancer cell. In addition, investigation of transcriptional and postranscriptional mechanisms regulate S100 expression as well as expression of these protein in different cancer cells also required.

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